Relative peak exercise oxygen pulse is related to sudden cardiac death, cardiovascular and all-cause mortality in middle-aged men

Jari A. Laukkanen,[1,2] Claudio Gil Soares de Araújo,[3] Sudhir Kurl,[1] Hassan Khan,[4] Sae Y Jae,[5] Marco Guazzi,[6] Setor K. Kunutsor[7]

[1]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland
[2]Central Finland Hospital District, Department of Internal Medicine, Jyväskylä, Finland
[3]Exercise Medicine Clinic , Rio de Janeiro, RJ, Brazil
[4]Emory University, Atlanta, GA, US
[5]Department of Sports Informatics, University of Seoul, Seoul, South Korea
[6]Department of Biomedical Sciences for Health, Cardiology University Department, University of Milano, Milan, Italy
[7]School of Clinical Sciences, University of Bristol, Southmead Hospital, Bristol, UK

Address for Correspondence:
Jari A. Laukkanen, Institute of Public Health and Clinical Nutrition, School of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland, FAX +358-17-162936, Tel +358-17-162950, E-mail: jariantero.laukkanen@uef.fi

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ABSTRACT

Background: Preliminary evidence suggests that peak exercise oxygen pulse (peO_2p) - peak oxygen uptake/heart rate, a variable obtained during maximal cardiopulmonary exercise testing and a surrogate of stroke volume, is a predictor of mortality. We aimed to assess the associations of peO_2p with sudden cardiac death (SCD), fatal coronary heart disease (CHD) and cardiovascular disease (CVD), and all-cause mortality.

Design: A prospective study

Methods: Peak exercise O_2 pulse was assessed in a maximal cycling testing at baseline in 2,227 middle-aged men of the Kuopio Ischemic Heart Disease cohort study using expired gas variables and electrocardiograms. Relative peO_2p was obtained by dividing the absolute value by body weight.

Results: During a median follow-up of 26.1 years 1,097 died; 220 SCDs, 336 fatal CHDs and 505 fatal CVDs. Relative peO_2p (mean 19.5 (4.1) mL per beat-1·kg-1·102) was approximately linearly associated with each outcome. Comparing extreme quartiles of relative peO_2p, hazard ratios (HRs) (95% CIs) for SCD, fatal CHD and CVD, and all-cause mortality on adjustment for cardiovascular risk factors were 0.55 (0.36-0.83), 0.58 (0.42-0.81), 0.60 (0.46-0.79), and 0.59 (0.49-0.70) respectively (P<0.001 for all). The HRs were unchanged on further adjustment for C-reactive protein and use of beta-blockers. Addition of relative peO_2p to a CVD mortality risk prediction model significantly improved risk discrimination (C-index change=0.0112; P=0.030).

Conclusion: Relative peO_2p measured during maximal exercise was linearly and inversely associated with fatal cardiovascular and all-cause mortality events in middle-aged men. Additionally, relative peO_2p provided significant improvement in CVD mortality risk assessment beyond conventional risk factors.

Keywords: peak exercise oxygen pulse; cardiopulmonary exercise testing; risk prediction; sudden cardiac death; cardiovascular diseases; all-cause mortality

Introduction

Cardiorespiratory or aerobic fitness, as measured by peak oxygen uptake (VO_2), has been one of the most widely examined CPX variables, particularly as it relates to functional capacity and human performance.[1, 2] In previous cohort studies, peak VO_2 has been shown to be inversely and independently associated with incident cardiovascular disease (CVD) events, cardiovascular and total mortality.[3-7] Evidence also suggests that peak VO_2 adds additional prognostic value beyond established risk factors in predicting vascular disease and mortality risk.[3, 8, 9]

Stroke volume response is one of the most important measures of cardiac performance during exercise.[10, 11] Exercise oxygen (O_2) pulse, a surrogate for stroke volume (SV), has emerged as an important variable which is obtained during cardiopulmonary exercise testing (CPX). Peak exercise oxygen pulse (peO_2p) is expressed as O_2 consumed per heart beat at maximal CPX and it is related to the risk of cardiovascular events.[12]

There is evidence to show that a high peO_2p is inversely related to all-cause mortality.[10, 13] However, data on the value of utilizing peO_2p as a risk assessment tool for serious and specific adverse events such as sudden cardiac death (SCD) and fatal coronary heart disease (CHD) are lacking. Although in the literature, peO2p is often expressed by its absolute value (i.e. mL/beat), its magnitude is obviously related to body dimensions. Thus ideally, similarly to peak VO_2, it should be expressed in relative form, that is, by dividing its absolute value by body weight.[11] Given the relative ease at which this exercise testing variable can be assessed noninvasively using expired gases analysis, it will be clinically relevant to know if peO_2p is a significant risk marker for fatal cardiovascular events and if it adds additional information beyond well-established cardiovascular risk factors. Our primary aim was to assess the nature and magnitude of the associations of relative peO_2p with the risk of SCD, fatal CHD and CVD events, and all-cause mortality using a population-based prospective cohort Finnish study . A secondary aim was to evaluate whether addition of relative peO2p measurements to conventional cardiovascular risk factors could improve the prediction of CVD mortality.

Methods

Study population

The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology were used in this study (**Appendix**).[14] Data analysis was undertaken in participants of the Finnish Kuopio Ischemic Heart Disease (KIHD) risk factor study, a prospective general population-based cohort study which aimed to study related risk factors for atherosclerotic CVD and other related chronic disease outcomes to aerobic performance. Detailed description of the study design, objectives, and sampling strategy has been previously reported.[15] The KIHD cohort was recruited from a representative sample of 3,433 men aged 42-61 years who were living in the city of Kuopio (Finland) and its surrounding communities. Of this number, 3,235 men were found to be eligible for inclusion and 2,682 (82.9%) volunteered to participate in the study. Baseline examinations were performed between March 1984 and December 1989. For the current analysis, 2,227 men with complete information on relative peO_2p, relevant covariates, and fatal outcomes were included. The medical ethics committee of the University of Eastern Finland approved the study protocol which was conducted in accordance with the Declaration of Helsinki. All study participants provided written informed consent.

Assessment of peak oxygen pulse

All participants underwent a morning symptom-limited cycling exercise testing.[16] with breath-by-breath respiratory gas analysis (Medical Graphics, US). Peak VO_2 was assessed as previously described[5, 16] and peO_2p was calculated by dividing the measured peak VO_2 by the maximum exercise heart rate, obtained from electrocardiogram, and was expressed in mL/beat. To remove the influence of body weight on the magnitude of peO_2p, values of peO_2p were then divided by weight in kilograms to yield relative

peO_2p. All results were multiplied by 100 for easier readability, as previously described.[11, 17] To ensure safety, all tests were supervised by experienced physician and nurse.

Assessment of covariates

Baseline data were obtained by history, questionnaire administration, physical examinations, and measurements as detailed elsewhere.[18, 19] Fasting cholesterol contents of serum lipoprotein fractions, triglycerides, plasma glucose, and serum high sensitivity C-reactive protein (hsCRP) were obtained from analysis of blood samples. Smoking, prevalent diseases, and regular and current use of medications were assessed by standardized self-administered questionnaires.[18] Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory. Resting blood pressure was measured before the CPX with a random-zero sphygmomanometer. History of CHD was based on a previous myocardial infarction, angina pectoris, use of nitroglycerin for chest pain once a week or more frequently or typical chest pain. The amount of physical activity was assessed from a 12-month physical activity history modified from the Minnesota Leisure-Time Physical Activity Questionnaire,[20] and expressed in kJ/day.[16]

Ascertainment of outcomes

All SCD, fatal CHD and CVD, and all-cause mortality events were ascertained from hospital documents, discharge lists, death certificates, informant interviews, health practitioner questionnaires, study electrocardiograms, medico-legal reports, and vital statistics offices from study enrollment through to the end of 2014. The diagnostic classification of SCDs was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings, and history of CHD plus clinical findings and information from hospital and paramedic staff, details of which have been previously described.[5, 21, 22] CVD deaths were coded using the Tenth International Classification of Diseases codes. Documents were cross-checked in detail by two physicians.

Statistical analysis

Baseline characteristics of study participants were summarized using descriptive statistics (i.e., means, medians, and percentages). Cross-sectional associations of relative peO_2p with risk markers were assessed by calculating age-adjusted partial correlation coefficients. Hazard ratios (HRs) with 95% confidence intervals (CIs) for SCD, fatal CHD and CVD events, and all-cause mortality were calculated using Cox proportional hazard models after confirmation of the proportionality-hazards assumption using Schoenfeld residuals. The shape of the association between relative peO_2p and each fatal outcome was characterized by calculating the HRs within quartiles of baseline relative peO_2p and plotting these against the mean values of relative peO_2p within each quartile using floating variances as described previously.[23, 24] We modelled our exposure as both continuous (per standard deviation, SD increase) and categorical (quartiles) variables. Hazard ratios were progressively adjusted for (i) age (Model 1); (ii) systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), smoking status, alcohol consumption, prevalent CHD, history of diabetes mellitus, and amount of physical activity (Model 2); and (iii) hsCRP and use of beta-blockers (Model 3). Subgroup analyses were performed using interaction tests to assess statistical evidence of effect modification by relevant clinical characteristics. To assess whether adding information on relative peO_2p to documented established risk factors is associated with improvement in prediction of CVD mortality risk, we calculated measures of discrimination for censored time-to-event data (Harrell's C-index[25]) and reclassification.[26, 27] To investigate the change in C-index, we added relative peO_2p to a CVD mortality risk prediction model (i.e., age, SBP, history of diabetes, total cholesterol, HDL-C, and smoking). Reclassification analysis was restricted to the first 10 years and was assessed using the net-reclassification-improvement (NRI).[26, 27] Given that we used CVD mortality as the outcome, we followed European guidelines[28] to determine clinically meaningful risk categories. Reclassification analyses was based on predicted 10-year CVD mortality risk categories of low (<1%),

intermediate (1 to <5%), and high (≥5%) risk. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, US).

Results

Baseline characteristics and correlates of relative peO_2p

The baseline mean (standard deviation) age and relative peO_2p were 53 (5) years and 19.5 (4.1) mL per $beat^{-1}.kg^{-1}.10^2$, respectively (**Table 1**). Relative peO_2p was weakly-to-moderately inversely correlated with age, alcohol consumption, physical measurements (body mass index, blood pressure, and resting heart rate), lipids (total cholesterol and triglycerides), fasting plasma glucose, and hsCRP. There was a relatively weak positive correlation of relative peO_2p with regular physical activity (r = 0.08), and HDL-C (r = 0.22) (**Table 1**). Values of relative peO_2p were lower in the presence of history of CHD, hypertension, diabetes, current smoking and use of antihypertensives.

Relative peO_2p and mortality

During a median (interquartile range) follow-up of 26.1 (19.1-28.1) years 1,097 subjects died (49.2% of study's sample), with a total of 220 SCDs, 336 fatal CHDs, and 505 fatal CVDs. In analyses adjusted for several established risk factors (age, SBP, total cholesterol, HDL-C, smoking status, alcohol consumption, prevalent CHD, history of diabetes mellitus, and physical activity), relative peO_2p was approximately linearly and inversely associated with SCD, fatal CHD, fatal CVD, and all-cause mortality (*P<0.001*) (**Figure 1**). **Table 2** summarizes the HRs (95% CIs) of relative peO_2p with each fatal outcome assessed. In age-adjusted analysis, the HRs (95% CIs) for SCD, fatal CHD, fatal CVD, and all-cause mortality per 1 SD increase in relative peO_2p were 0.63 (0.54-0.73), 0.63 (0.56-0.71), 0.66 (0.60-0.73), and 0.73 (0.68-0.78) (*P<0.001*), respectively. The associations (HRs) remained consistent and significant after adjustment for several established cardiovascular risk factors plus hsCRP and use of beta-blockers; 0.76 (0.65-0.89), 0.75 (0.66-0.86), 0.77 (0.70-0.86), and 0.80 (0.74-0.86**),** respectively. Alternatively,

comparing the top versus bottom quartile of relative peO_2p, the age-adjusted HRs (95% CIs) for SCD, fatal CHD, fatal CVD, and all-cause mortality were 0.35 (0.24-0.53), 0.39 (0.28-0.53), 0.42 (0.33-0.54), and 0.49 (0.41-0.58) (*P<0.001*), respectively, and also significant after adjustment for several established cardiovascular risk factors with hsCRP and use of beta-blockers, the corresponding hazard ratios were 0.54 (0.36-0.82), 0.57 (0.41-0.80), 0.61 (0.47-0.80), and 0.61 (0.51-0.73), respectively (**Table 2**). The associations were generally not modified by several clinically relevant characteristics (**Figures 2 and 3**), except for suggestion of effect modification by history of CHD for the association of relative peO_2p with SCD. Though the associations were in the same direction, stronger protective associations were observed in presence of a history of CHD. Peak O2p was associated with SCD, fatal CHD, fatal CVD and all-cause mortality among men who were not using b-blockers as well as among those were using beta-blockers as shown in **Figure 2 and 3** and this relationship was not modified by the use of beta-blockers.

Relative peO_2p and CVD mortality risk prediction

A CVD mortality risk prediction model containing established risk factors yielded a C-index of 0.7009 (95% CI: 0.6784-0.7234). After addition of information on relative peO_2p, C-index changed to 0.7121 (95% CI: 0.6899-0.7344), representing a significant increase of 0.0112 (95% CI: 0.0011 to 0.0214; *P*=0.030). However, there was no improvement in the classification of participants into predicted 10-year CVD mortality risk categories (NRI: 4.18%, -3.24 to 11.61%; *P*=0.269).

In an approach to compare the predictive ability of relative peO_2p with peak VO_2, which has been consistently shown to improve CVD risk prediction above that of traditional cardiovascular risk factors,[3, 8, 29] peak VO_2 measurements was added to the CVD mortality prognostic model. There was a C-index change of 0.0348 (95% CI: 0199 to 0.0497; $P < 0.001$) and it yielded a NRI of 16.40% (8.21 to 24.59%; $P < 0.001$) for the predicted 10-year CVD mortality risk categories.

Furthermore, in a prediction model containing established risk factors plus peak VO_2, the C-index change was 0.0028 (95% CI: -0.0011 to 0.0068; *P*=0.161) on addition of information on relative peO_2p

and NRI was 1.15% (-3.17 to 5.48%; *P*=0.601).

Discussion

In this population-based prospective cohort study of apparently healthy Finnish men with a median follow-up period of over 25 years, we found approximately significant, linear and inverse associations of relative peO_2p with distinct fatal cardiovascular and all-cause mortality outcomes. The associations were independent of several established and emerging cardiovascular risk factors. The magnitude and directions of the associations were generally consistent across several clinically relevant subgroups including the use of beta-blockers (yes vs. no), except by the possible effect modification by history of CHD on relative peO_2p and SCD association. The stronger inverse association between relative peO_2p and SCD risk in men with a prevalent history of CHD may corroborate existing evidence that exercise training has more beneficial effects on adverse outcomes in individuals with pre-existing cardiometabolic disease.[30] Furthermore, findings from the assessments of improvements in risk discrimination indicate that relative peO_2p provides a significant improvement in CVD mortality risk prediction but not beyond that provided by established cardiovascular risk factors and peak VO_2. Further analyses showed that the improvement provided by peak VO_2 assessment in prediction of CVD mortality risk was better than that of relative peO_2p, which further confirms the superiority of peak VO_2 as a prognostic tool.

The concept of oxygen pulse is more than 100 years old.[31] Notwithstanding, studies on the associations of peO_2p with cardiovascular and mortality outcomes are limited and have been based in populations with smaller sample sizes or with pre-existing disease and have rarely taken in account the body weight, i.e. the relative peO_2p. In a French study that compared the long-term prognostic value of peO_2p and peak VO_2 in 178 patients with chronic heart failure, peO_2p was found to have a lower prognostic value for survival compared with peak VO_2,[12] however, in a larger sample of 998 heart failure patients[32], the age-predicted peO_2p (an indirect way to adjust peO_2p per body weight) has complemented peak O_2 in the prediction of risk for mortality, while Lavie et al[33] studied 209 patients with mild-to-

moderate heart failure and found that peO_2p/lean body mass outperforms peak O_2. These apparently contradictory findings may be explained by different ways to analyze peO_2p data, either as an absolute value or in same way related to body weight or lean body mass. Our data have shown that relative peO_2p is independently associated with several long-term cause-specific cardiovascular mortality outcomes as well as all-cause mortality in a general middle-aged population. Additionally, we showed that relative peO_2p provided prognostic value for CVD mortality beyond established risk factors, although, there was no significant improvement beyond that of peak VO_2. Considering that these two CPX variables are mathematically related and that both improve with exercise training,[34] these relatively similar results are not surprising. Indeed, if relative peO_2p or peak VO_2 will be a better prognostic indicator may vary according to the characteristics of subjects being studied and the outcomes that are being examined.[35, 36] Considering the easiness in determining relative peO_2p from expired gas analysis, it seems quite logical to include this result in CPX reports.

There is growing evidence on the clinical usefulness of CPX variables as supported by several guidelines.[37, 38] Notwithstanding, incorporation of these CPX variables in clinical practice is still limited. Currently, peak VO_2, VO_2 at ventilatory/anaerobic threshold, and ventilatory efficiency (i.e., minute ventilation/carbon dioxide production (V_E/VCO_2) relationship are the only three CPX variables that have been consistently proven to show prognostic significance .[39] Peak exercise oxygen pulse, is gaining attention as a clinically useful variable and can easily be obtained during CPX and computed as the ratio of maximum values of VO_2 and heart rate. Additionally, interpretation of exercise oxygen pulse curves could also be clinically relevant, since abnormal and flat oxygen pulse curves during CPX have been shown to reflect left ventricular dysfunction[40] and myocardial ischemia[41, 42] or fibrosis[43]. The prognostic utility of the peO_2p curves deserves further study.

Strengths and limitations

We have reported the first prospective evaluation of the associations of relative peO_2p, i.e. peO_2p/body weight, with the risk of major fatal cardiovascular events and all-cause mortality outcomes in a general population setting. The KIHD cohort was characterised by a high participation rate and no losses to follow-up were recorded, which minimised potential selection bias. Additionally, outcomes were confirmed and validated.[5, 8] We have utilized comprehensive analysis which included adjustment for several lifestyle and biological markers, assessment of the dose-response relationships, subgroup analyses, and risk prediction analyses. Oxygen pulse is an indicator of SV response to exercise that might be influenced by body dimensions and heart size,[44] and adjustments for body size and/or weight should be ideally included in studies on peO_2p, especially if data from male and female subjects are to be compared in different populations. The lack of control for confounding variables such as body weight might have limited the interpretation of previous reports.[10, 42] In our analyses, we used a relative peO_2p which took into account body weight, thus strengthening the validity of the results.

When interpreting the results, some limitations should be considered. The KIHD study included middle-aged Caucasian men from eastern Finland, so extrapolation to other populations and age groups, and particularly for women, might not be valid and more research is needed in this regard. Though we adjusted for a comprehensive panel of covariates, residual confounding remains a potential alternative explanation for our findings, due to the observational design of the study. According to the Fick equation, O_2 pulse equals the product of SV and arterio-venous oxygen difference, whiles O_2 pulse tends to exhibit a quasi-linear increase throughout maximal exercise.[11] We have previously shown that left ventricular diastolic and systolic diameter are directly associated with peO_2p.[10] Even though direct measurements of SV were not available in the current study, there is convincing evidence that O_2 pulse correlates well with direct measurements of SV during submaximal and maximal exercise in healthy and unhealthy subjects of different age groups.[40, 44-46]

In conclusion, the findings of this large prospective cohort study in middle-aged Finnish men with long-term follow-up indicate strong linear and inverse associations of relative peO_2p with fatal cardiovascular and all-cause mortality events. Additionally, the incorporation of relative peO_2p during a maximal cycling CPX provides significant improvement in CVD mortality risk assessment beyond several conventional risk factors.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Table 1. Baseline participant characteristics and correlates of relative peak exercise oxygen pulse

	Mean (SD), median (IQR), or n (%)	Partial correlation r (95% CI)[a]	Absolute difference (95% CI) in values of relative peO_2p per 1 SD higher or compared to reference category of correlate[b]
Peak exercise oxygen pulse (mL/beats)	15.5 (3.4)	-	-
Relative peO_2p (mL/beats/kg)	19.5 (4.1)	-	-
Questionnaire/Prevalent conditions			
Age at survey (years)	53 (5)	-0.15 (-0.19, -0.11)***	-0.62% (-0.79, -0.46)***
Alcohol consumption (g/week)	74.3 (122.2)	-0.10 (-0.14, -0.06)***	-0.40% (-0.56, -0.23)
History of diabetes			
No	2,149 (96.5)	-	Ref
Yes	78 (3.5)	-	-1.92% (-2.83, -1.00)***
Smoking status			
Other	1,530 (68.7)	-	Ref
Current	697 (31.3)	-	-0.64% (-1.00, -0.28)**
History of hypertension			
No	1,568 (70.4)	-	Ref
Yes	659 (29.6)	-	-0.68% (-1.05, -0.31)**
History of CHD			
No	1,701 (76.4)	-	Ref
Yes	526 (23.6)	-	-1.38% (-1.78, -0.98)***
Use of anti-hypertensives			
No	1,762 (79.1)	-	Ref
Yes	465 (20.9)	-	-0.67% (-1.09, -0.26)*
Use of beta-blockers			
No	1,847 (82.9)	-	Ref
Yes	380 (17.1)	-	-0.13% (-0.59, 0.32)
Physical measurements			
BMI (kg/m^2)	26.9 (3.4)	-0.33 (-0.37, -0.29)***	-1.33% (-1.49, -1.17)***
Weight (kg)	80.3 (11.8)	-0.31 (-0.34, -0.27)***	-1.24% (-1.40, -1.08)***
SBP (mmHg)	134 (17)	-0.17 (-0.21, -0.13)***	-0.68% (-0.85, -0.52)***
DBP (mmHg)	89 (10)	-0.19 (-0.23, -0.15)***	-0.77% (-0.93, -0.60)***
Physical activity (kj/day)	1,545 (1,408)	0.08 (0.04, 0.12)**	0.33% (0.17, 0.50)***
Heart rate (beats/min)	62.4 (10.8)	-0.38 (-0.42, -0.34)***	-1.54% (-1.71, -1.38)***
Lipid markers			
Total cholesterol (mmol/l)	5.91 (1.07)	-0.05 (-0.10, -0.01)*	-0.22% (-0.39, -0.05)*
HDL-C (mmol/l)	1.29 (0.30)	0.22 (0.18, 0.26)***	0.89% (0.72, 1.05)***
Triglycerides (mmol/l)	1.09 (0.79-1.54)	-0.25 (-0.29, -0.21)***	-1.02% (-1.18, -0.85)***
Metabolic, renal markers, and inflammatory markers			
Fasting plasma glucose (mmol/l)	5.33 (1.20)	-0.17 (-0.21, -0.12)***	-0.67% (-0.83, -0.50)***
Serum creatinine (μmol/1)	89.7 (21.7)	-0.02 (-0.07, 0.02)	-0.09% (-0.27, 0.08)
Estimated GFR (ml/min/1.73 m^2)	87.1 (17.2)	-0.03 (-0.08, 0.01)	-0.14% (-0.32, 0.04)
High sensitivity CRP	1.25 (0.69-2.37)	-0.27 (-0.31, -0.23)***	-1.10% (-1.26, -0.94)***

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; peO_2p, peak exercise oxygen pulse; SD, standard deviation; SBP, systolic blood pressure; [a], Partial correlation coefficients between relative peO_2p and the row variables;. [b], Absolute change in values of relative peO_2p per 1-SD increase in the row variable (or for categorical variables, the absolute difference in mean values of relative peO_2p for the category versus the reference) adjusted for age; asterisks indicate the level of statistical significance: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$

Table 2. Associations of relative peak exercise oxygen pulse with sudden cardiac death, fatal coronary heart disease, fatal cardiovascular disease, and all-cause mortality

Models **Relative peak oxygen pulse (ml/beats/kg)**	**Sudden cardiac death**		**Fatal coronary heart disease**		**Fatal cardiovascular disease**		**All-cause mortality**	
	220 cases		**336 cases**		**505 cases**		**1,097 cases**	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p value*
Model								
Per 1 SD increase	0.63 (0.54-0.73)	< 0.001	0.63 (0.56-0.71)	< 0.001	0.66 (0.60-0.73)	< 0.001	0.73 (0.68-0.78)	< 0.001
Quartile 1 (6.4-16.8)	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Quartile 2 (16.8-19.3)	0.62 (0.44-0.87)	0.005	0.65 (0.50-0.86)	0.002	0.65 (0.52-0.81)	< 0.001	0.70 (0.60-0.82)	< 0.001
Quartile 3 (19.3-21.9)	0.47 (0.32-0.68)	< 0.001	0.43 (0.32-0.59)	< 0.001	0.47 (0.37-0.60)	< 0.001	0.60 (0.51-0.71)	< 0.001
Quartile 4 (21.9-42.7)	0.35 (0.24-0.53)	< 0.001	0.39 (0.28-0.53)	< 0.001	0.42 (0.33-0.54)	< 0.001	0.49 (0.41-0.58)	< 0.001
Model 2								
Per 1 SD increase	0.77 (0.66-0.90)	0.001	0.76 (0.67-0.86)	< 0.001	0.77 (0.69-0.85)	< 0.001	0.79 (0.74-0.85)	< 0.001
Quartile 1 (6.4-16.8)	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Quartile 2 (16.8-19.3)	0.71 (0.51-1.01)	0.054	0.75 (0.57-0.99)	0.041	0.72 (0.58-0.91)	0.005	0.74 (0.63-0.86)	< 0.001
Quartile 3 (19.3-21.9)	0.63 (0.44-0.92)	0.016	0.57 (0.42-0.79)	0.001	0.60 (0.46-0.77)	< 0.001	0.69 (0.59-0.82)	< 0.001
Quartile 4 (21.9-42.7)	0.55 (0.36-0.83)	0.005	0.58 (0.42-0.81)	0.001	0.60 (0.46-0.79)	< 0.001	0.59 (0.49-0.70)	< 0.001
Model 3								
Per 1 SD increase	0.76 (0.65-0.89)	0.001	0.75 (0.66-0.86)	< 0.001	0.77 (0.70-0.86)	< 0.001	0.80 (0.74-0.86)	< 0.001
Quartile 1 (6.4-16.8)	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Quartile 2 (16.8-19.3)	0.73 (0.52-1.02)	0.067	0.76 (0.58-1.00)	0.047	0.74 (0.59-0.93)	0.009	0.76 (0.65-0.89)	0.001
Quartile 3 (19.3-21.9)	0.63 (0.43-0.92)	0.016	0.57 (0.42-0.78)	< 0.001	0.60 (0.47-0.77)	< 0.001	0.70 (0.60-0.83)	< 0.001
Quartile 4 (21.9-42.7)	0.54 (0.36-0.82)	0.004	0.57 (0.41-0.80)	0.001	0.61 (0.47-0.80)	< 0.001	0.61 (0.51-0.73)	< 0.001

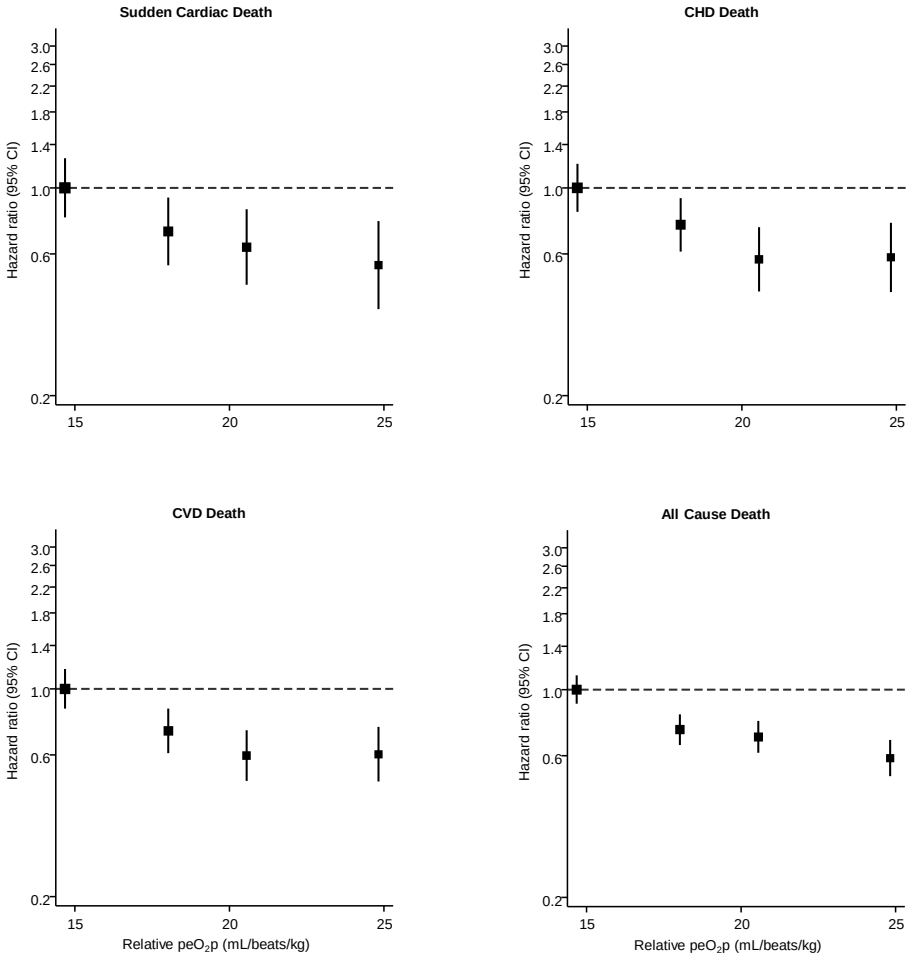
Model 1: adjusted for age

Model 2: Model 1 plus systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, alcohol consumption, prevalent coronary heart disease, history of diabetes mellitus, and physical activity

Model 3: Model 2 plus high sensitivity C-reactive protein and use of beta-blockers

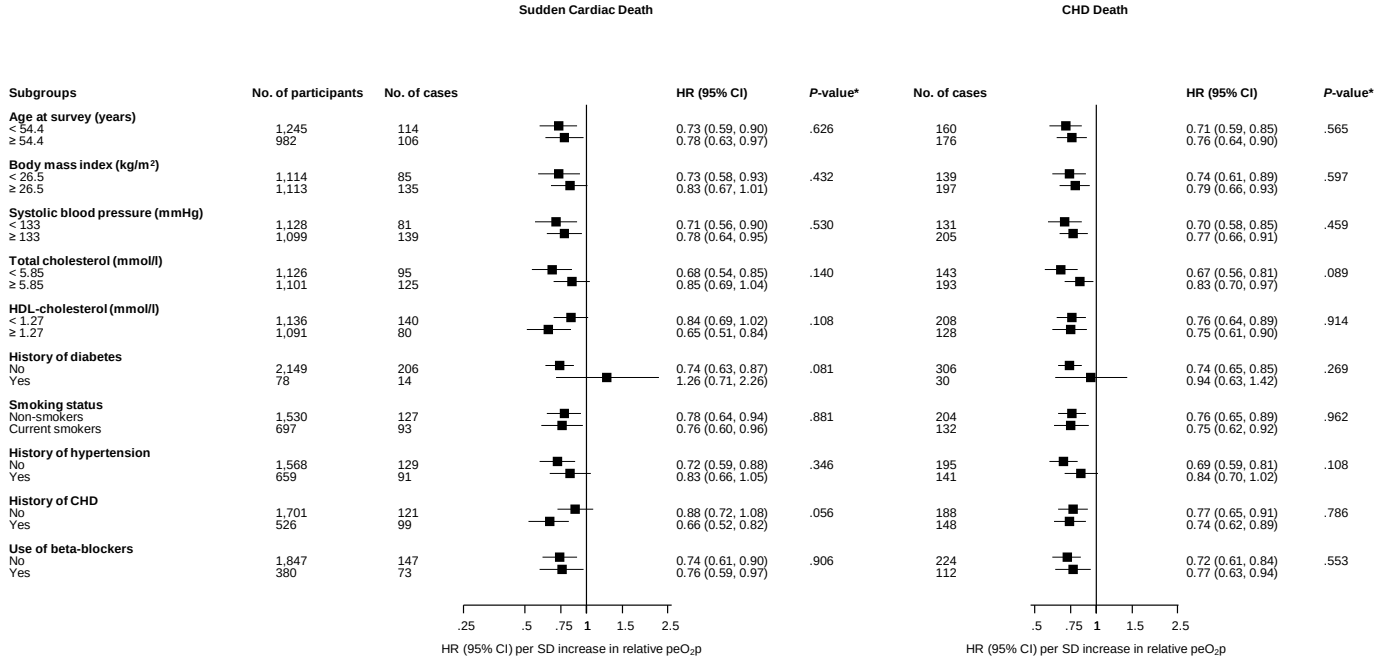
Figure Titles and Legends

Figure 1. Hazard ratios for sudden cardiac death, fatal coronary heart disease, fatal cardiovascular disease, and all-cause mortality by quartiles of relative peak exercise oxygen pulse



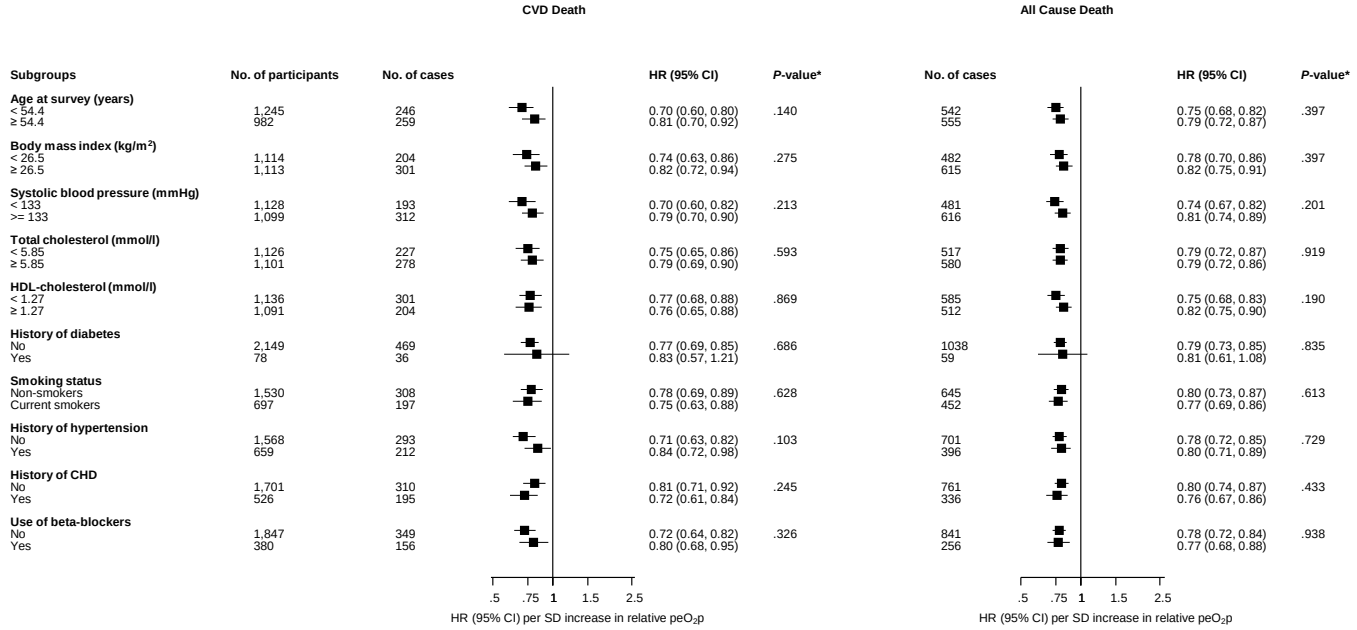
Hazard ratios were adjusted for age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, alcohol consumption, prevalent coronary heart disease, history of diabetes mellitus, and physical activity

Figure 2. Hazard ratios per one standard deviation change (4.1 mL per beat-1·kg-1·10^2) in relative peak exercise oxygen pulse for sudden cardiac death and fatal coronary heart disease by several participant characteristics



Hazard ratios were adjusted for age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, alcohol consumption, prevalent coronary heart disease, history of diabetes mellitus, and physical activity; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; peO_2p, peak exercise oxygen pulse; SD, standard deviation; *, *p*-value for interaction; cut-offs for age, body mass index, systolic blood pressure, total cholesterol, and HDL cholesterol are based on median values.

Figure 3. Hazard ratios per one standard deviation change (4.1 mL per beat^{-1}·kg^{-1}·10^{2}) in relative peak exercise oxygen pulse for cardiovascular and all-cause mortality by several participant characteristics



Hazard ratios were adjusted for age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, alcohol consumption, prevalent coronary heart disease, history of diabetes mellitus, and physical activity; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; peO_2p, peak exercise oxygen pulse; SD, standard deviation; *, *p*-value for interaction; cut-offs for age, body mass index, systolic blood pressure, total cholesterol, and HDL cholesterol are based on median values.